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(54) Title: NEUROPROTECTIVE ACTIVITY OF ACTIVATED PROTEIN C IS INDEPENDENT OF ITS ANTICOAGULANT ACTIVITY

(57) Abstract: Activated protein C (APC), prodrug, and/or a variant thereof may be used as an inhibitor of apoptosis or cell death and/or a cell survival factor, especially for stressed or injured cells or tissues of the nervous system including subjects with neurodegenerative disorders. Novel biological functions (e.g., neuroprotection) can be independent or separated from inhibition of clotting or inflammation, and other biological properties of APC (e.g., antithrombotic activity, ability to reduce NFkB-regulated gene expression). It can be used in the treatment of disease or other pathological conditions by at least inhibiting the p53-dependent and/or caspase-3-dependent pro-apoptotic signaling pathways in stressed or injured cells. Thus, APC, prodrugs, and variants thereof (e.g., APC protease domain mutants with reduced anti-coagulant activity) are prototypes of a class of agents for preventing apoptosis or cell death and/or promoting cell survival by direct action on brain cells. New protein C and/or APC variants with reduced anticoagulant activity may be selected thereby.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/38764

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 49/00;A01N 1/02;C12Q 1/68; G01N 33/53; C12P 1/00; C12N 5/02; C07K 7/00, 17/00  
US CL : 424/9.1; 435/2, 6, 7.2,41, 325; 530/300, 350

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/9.1; 435/2, 6, 7.2,41, 325; 530/300, 350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
PALM, WEST , EAST, NPL

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
STN, USPATFULL, MEDLINE, BIOSIS, CAPLUS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/0028199 A1 (GRIFFIN et al) 07 March, 2002 (07.03.2002), page 4, right column, page 5, page 6, left column, page 7-8 (compositions).	1-20
X	US 2004/0033517 A1 (RUF et al) 19 June 2004 (19.06.2004), page 21, both columns, page 23, right column, page 31(composition), page 32-35, example 1.	21-27
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E		

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier application or patent published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 December 2004 (04.12.2004)

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/38764

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claim Nos.: 28  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claim 28 recites a peptide sequence without any sequence identifier. Therefore, search can not be performed in a meaningful way.
2.  Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

  

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.